Usefulness of adjunctive alpha1-adrenergic antagonists after single extracorporeal shock wave lithotripsy session in ureteral stone expulsion

Abdellatif Janane, MD; Abdelaziz Hamdoun, MD; Fouad Hajji, MD; Youssef Dakkak, MD; Mohamed Ghadouane, MD; Ahmed Ameur, MD; Mohamed Abbar, MD

Department of Urology, University Military Hospital Mohammed V. Rabat, Morocco

Cite as: *Can Urol Assoc J* 2014;8(1-2):e8-11. http://dx.doi.org/10.5489/cuaj.1261
Published online January 14, 2014.

Abstract

Introduction: We evaluate the efficiency of α-adrenergic antagonists on stone clearance after extracorporeal shock wave lithotripsy (ESWL) in patients with lower ureteral stones.

Methods: A total of 356 patients with solitary lower ureteral stones who underwent single ESWL sessions were divided into 2 groups. Group 1 received our standard medical therapy, and Group 2 was treated with 0.4 mg/day tamsulosin for a maximum of 2 weeks. All patients were re-evaluated with plain film radiography and ultrasound each week during the treatment period. A computed tomography scan was systematically performed 3 months after ESWL.

Results: In total, 82 of the 170 patients in Group 1 (48.2%) and 144 of the 186 patients in Group 2 (77.4%) ($p = 0.002$) were stone-free. Among the patients with stones 10 to 15 mm in diameter, the stone-free rate was 38.4% in Group 1 and 77.1% in Group 2 ($p = 0.003$). Average stone expulsion time was 10.6 days and 8.4 days in Groups 1 and 2, respectively. Ureteral colic occurred in 40 patients (23.5%) in Group 1, but only in 10 patients (5.3%) in Group 2 ($p = 0.043$). The only side effect of tamsulosin was slight dizziness in 5 of the 186 patients in Group 2 (2.6%).

Conclusion: Adjunctive therapy with α1-adrenergic antagonists after ESWL is more efficient than, and equally as safe as, lithotripsy alone to manage patients with lower ureteral stones. The adding of α-blockers is more reliable and helpful for stones with a large dimension, and can also decrease stone elimination time and episodes of ureteral colic.

Introduction

Several authors have proposed the use of α-blockers to facilitate lower ureteral stone (juxtavesical tract and ureterovesical junction) passage and expulsion.[1,2] Extracorporeal shock wave lithotripsy (ESWL) is accepted as the first-line treatment for patients with ureteral stones; however, this approach does not seem to work efficiently when the stone size increases. Recently, ESWL has been reconsidered for the treatment of larger ureteral stones. Some authors have found positive results in accelerating lower ureteral stone passage using α-adrenergic antagonists on the basis that α1-adrenergic receptors play an important physiological role in distal ureteral passage.[1,6] To our knowledge, there are no comparative papers that investigate the effectiveness of different expulsive medical therapies (EMT). We carry out a comparative study to evaluate the safety and efficacy of α-adrenergic antagonists for the ureteral stone passage.

Methods

Between January 2008 and December 2012, 356 patients with lower ureteral stones were evaluated by physical examination, serum creatinine measurement, plain abdominal X-rays, intravenous pyelography and abdominal ultrasound. Patients were excluded from the study if they had any of the following: urinary tract infection, multiple stones, severe hydronephrosis, solitary kidney, congenital urinary anomalies or previous ureteral surgery. Patients with severe obesity, pregnancy, lactation or previous treatment with α-adrenergic antagonists were also excluded. In the end, 356 patients were enrolled in the study.

Patients were treated using a Storz medical lithotripter (MODULITH° SLX-F2). The number of shocks given to each patient was decided empirically according to the diameter of the stone. Patients were in the supine position, and no analgesics were used during ESWL. After ESWL, the patients were assigned to 2 groups by simple random allocation, and placebo-controlled medical treatment was initiated immediately and continued for a maximum of 2 weeks, or until an alternative treatment was applied. Standard treatment of 25 mg diclofenac was given 3 times daily to Group 1, the

control group. Group 2 received the standard medical treatment in addition to 0.4 mg tamsulosin (α1-adrenergie antagonist) once daily. Furthermore, all patients were instructed to drink a minimum of 2 L of water daily and were asked to keep a diary on ureteral colic, stone expulsion and the side effects of medical therapy. Follow-up included clinical examination, abdominal ultrasound and/or intravenous pyelography repeated every week after lithotripsy. A computed tomography (CT) scan was systematically performed 3 months after ESWL.

Data were analyzed using SPSS 13.0 software (SPSS Inc., Chicago, IL).

Results

Group 1 included 66 women and 104 men, with a mean age of 43.4 ± 12.2 years (range: 17-65); Group 2 included 78 women and 108 men, with a mean age of 41.2 ± 12.4 years (range: 19-67). The stone diameter was 9.4 ± 3.0 and 9.2 ± 2.8 mm for Groups 1 and 2, respectively. The groups were not significantly different in their demographic and clinical characteristics (Table 1) ($p > 0.05$).

All patients underwent 1 session of ESWL. A mean of 3050 ± 266 shocks per patient in Group 1 was delivered at a mean voltage of 7.7 ± 0.6 kV, and a mean of 2900.0 ± 250 shocks per patient in Group 2 was delivered at a mean voltage of 7.9 ± 0.8 kV, with no significant difference between groups ($p > 0.05$). In total, 82 of the 170 patients in Group 1 (48.2%) and 144 of the 186 patients in Group 2 (77.4%) were stone free. The difference between groups was statistically significant ($p = 0.002$).

Among patients with stones 10 to 15 mm in diameter, we found a significant difference in the stone-free rate between the 2 groups (38.4% in Group 1 and 77.1% in Group 2; $p = 0.003$). In contrast, we found no significant difference in the stone-free rate among patients with stones 5 to 9 mm in diameter (64.4% in Group 1 and 76.8% in Group 2; $p = 0.305$). The average stone expulsion time for Groups 1 and 2 was 10.6 ± 1.6 days and 8.4 ± 1.8 days, respectively ($p < 0.001$). Ureteral colic occurred in 23.5% of patients in Group 1, but in only 5.3% of patients in Group 2 ($p = 0.041$). The only side effect of tamsulosin was slight dizziness in 5 of the 186 patients in Group 2 (2.6%).

Table 1. Demographic and clinical patient characteristics

	Group 1 (n=170)	Group 2 (n=186)
Mean age (year)	43.4 ± 12.2	41.2 ± 12.4
Mean weight (kg)	70.4 ± 5.2	72.4 ± 6.3
Stone diameter		
5-9 mm	68	83
10-15 mm	102	103
Mean diameter (mm)	9.4 ± 3.0	9.2 ± 2.8
Stone composition		
Whellite	98 (57.64%)	101 (54.30%)
Weddelite	59 (34.70%)	64 (34.40%)
Carbapatite	10 (5.88%)	15 (8.06%)
Brushite	3 (1.76%)	6 (3.22%)
Mean skin to stone distance (cm)	11.7 ± 1.9	12.4 ± 2.1
Stone location		
Upper calyces	26 (15.29%)	30 (16.12%)
Mid calyces	19 (11.17%)	23 (12.36%)
Renal pelvis	75 (44.11%)	79 (42.47%)
Lumbar ureter	50 (29.41%)	54 (29.03%)

Discussion

Ureteral calculi occupy a considerable place in daily urological practice. Of all urinary tract stones, 22% are ureteral, and 66% to 71% of these are located in the distal portion of the ureter. If the diameter of ureteral calculi is less than 6 mm, spontaneous passage is generally possible (35% to 58 %). Ureteral stones greater than 6 mm and less than 8 mm in diameter have a ≤12% chance to be spontaneously expelled.[1,2]

Due to the availability and the high success of the ESWL, this option represents the first-line therapy for lower ureteral calculi, but it implies a certain percentage of re-treatments. The major goal in treating patients with lower ureteral stones is achieving a stone-free state. Stone fragment expulsion after ESWL is probably not dissimilar to spontaneous passage.[3,5] Several variables play an incountournable role in the migration of calculi: stone size, intrinsic areas of narrowing within the ureter, ureteral peristalsis, and hydrostatic pressure of the column of urine proximal to the stone, edema, urinary tract infection, and spasm of the ureteral sire in which the stone is lodged.[4,6]

Edema, urinary tract infection, spasm and ureteral peristalsis can be modified by appropriate medical therapy. If the friction between the intraureteral wall and the stone decreases, ureteral relaxation occurs and promotes stone passage at the site of obstruction. Two factors that appear to be most useful in facilitating stone passage are increase in hydrostatic pressure proximal to the stone, and relaxation of the ureter in the region of the stone. The primary functional anatomical unit of the ureter is the ureteral smooth muscle cell. The sympathetic nervous system appears to modulate ureteral activity as shown by the presence of adrenergic receptors in the ureter.[5,7] Hancock has reported the presence of α- and β-adrenergic receptors in the human ureter.[8] Several studies have shown that the density of α1-adrenergic receptors in the ureteral smooth muscle cells is greater than that of other adrenergic receptors.[9] According to the general consensus, α-adrenergic receptor agonists tend to stimulate ureteral activity. Yet, α-adrenergic receptor agonists tend to inhibit ureteral activity. α-Adrenergic receptors are found in

trigone, prostatic urethra and ureters. These receptors cause contraction of the smooth muscles in these regions.[10] It is suggested that α-adrenergic stimulation reduces the volume of urine flow through the ureter and causes ureteral spasm.[2,10]

Treatment regimens involving alpha-adrenergic drugs promote ureteral smooth relaxation. Alpha1-adrenergic receptor antagonists have some degree of selectivity for the detrusor and distal ureter and have therefore been investigated for their capacity and their potential to promote and enhance stone passage and decrease renal pain.[10,11]

Resim and colleagues have reported the spontaneous passage of lower ureteral stones in 86.6% of patients who were treated with an α-adrenergic antagonist, and a significant difference in the stone-free rate between patients treated with tamsulosin and the control group.[12] Küpeli and colleagues found a favourable impact of 15-day tamsulosin treatment on the clearance of residual fragments after ESWL.[13] Porpiglia and colleagues also found that the stone-free rare was significantly greater with nifedipine and deflazacort supplementation than without it.[14]

In complete obstruction, signs of kidney injury and suffering parenchyma appear within 4 weeks. For this reason, urologists may wait up to 4 weeks before seeing if the calculi will pass spontaneously, provided that the patient is comfortable. Some studies with medical expulsive therapy (alfuzosin, doxazosin, terazosin) showed that 79% to 92% of stone expulsions occur within 15 days of therapy.[1,11]

In our study, 48.2% and 77.4% of patients who underwent ESWL alone and ESWL plus tamsulosin treatment, respectively ($p = 0.002$), were stone-free. For stones larger than 10 mm in diameter, however, the success rate was significantly greater in patients who underwent ESWL plus tamsulosin treatment compared with those receiving ESWL alone. This might be attributed to the effect of tamsulosin in improving the passage of larger fragments generated after ESWL. During ESWL, larger stones often generate larger fragments that migrate less easily. In such cases, tamsulosin could promote the passage of these fragments by increasing the intra ureteral flow and the intraureteral pressure gradient above the stone, or by decreasing the peristalsis above the stone. Regarding expulsion time, we observed stone passage after 10.6 days in Group 1 and 8.4 days in Group 2 ($p < 0.001$). Our results demonstrate that the use of tamsulosin significantly reduced expulsion times in comparison with the control group.

Ureteral stones usually cause severe colic pain as a result of increasing intraureteral pressure above the ureteral obstruction. The goal of treatment of ureteral colic is to relieve pain and release the ureteral obstruction.[15] Dellabella and colleagues have found that treatment with tamsulosin relieves ureteral colic pain, as indicated by significantly less analgesic use.[2] In our study, ureteral colic occurred in 23.5% of patients in Group 1, but in only 5.3% of patients in Group 2 ($p = 0.041$).

The only side effect of tamsulosin was slight dizziness in 5 of the 186 patients in Group 2 (2.6%), demonstrating that the tamsulosin probably decreased the frequency of peristaltic contractions within the ureter.

The side effects with tamsulosin treatment after ESWL were mild. In the study by Porpiglia and colleagues,[11] the incidence of side effects with adjunctive medication was 10%, while it was only 2.6% in our study. The rates of side effects, such as dizziness, rhinitis and diarrhea, have been reported to be 14.9%, 13.1% and 6.2%, respectively. However, these rates were recorded after at least 13 weeks of tamsulosin treatment for benign prostatic hyperplasia. In the present study, only 2.6% of patients receiving tamsulosin reported slight dizziness within the 2-week treatment period. However, this low number of side effects was probably due to the short follow-up period.

The current evidence suggest that medical expulsive therapy with α-blockers increases calculi ejection rates, diminishes the time of calculi elimination and lowers analgesia requirements for ilio-pelvic ureteral stones with and without ESWL for calculi <10 mm in diameter. A combination of corticosteroids for 5 days and α-blockers (15 days) could be more efficient than α-blockers alone.[10,15] Most randomized studies are small and single-centred, and limit the grade of recommendation. Therefore, large multicentre, randomized, placebo-controlled trials are needed.

Conclusion

We found that adjunctive therapy with α1-adrenergic antagonists after ESWL is more effective than lithotripsy alone, while it is equally safe. Our analysis also indicates that α1-blockers are more effective for calculi with larger diameters. In addition, adjunctive therapy with α1-blockers might significantly enhance stone expulsion rates and decrease stone elimination time and the number and intensity of ureteral colic episodes after ESWL.

Competing interests: Dr. Janane, Dr. Hamdoun, Dr. Hajji, Dr. Dakkak, Dr. Ghadouane, Dr. Ameur and Dr. Abbar all declare no competing financial or personal interests.

This paper has been peer-reviewed.

References

1. De Sio M, Autorino R, Di Lorenzo G, et al. Medical expulsive treatment of distal ureteral stones using tamsulosin: A single-center experience. *J Endo Urol* 2006;20:12-6. http://dx.doi.org/10.1089/end.2006.20.12
2. Dellabella M, Milanese G, Muzzonigro G. Efficacyoftamsulosin in the medical management of juxtavesical ureteral stones. *J Urol* 2003;170:2202-5. http://dx.doi.org/10.1097/01.ju.0000096050.22281.a7
3. Dellabella M, Milanese G, Muzzonigro G. Randomized trial of the efficacy of ramsutosin, nifedipine and phloroglucinol in medical expulsive therapy for distal ureter calculi. *J Urol* 2005;174:167-72. http://dx.doi.org/10.1097/01.ju.0000161600.54732.86

4. Malin JM Jr, Dcane RF, Boyarsky S. Characterization of adrenergic receptors in human ureter. *Br J Urol* 1970;42:171-4. http://dx.doi.org/10.1111/j.1464-410X.1970.tb10018.x
5. Menon M, Resnick MI. Urinary lithiasis: Etiology, diagnosis and medical management. In: Walsh PC, ed. *Campbell's Urology*. Philadelphia: Saunders; 2002:3227-9.
6. Georgiev MI, Ormanov DI, Vassilev VD, et al. Efficacy of tamsulosin oral controlled absorption system after extracorporeal shock wave lithotripsy to treat urolithiasis. *Urology* 2011;78:1023-6. http://dx.doi.org/10.1016/j.urology.2011.01.073
7. Miyatake R, Torniyama Y, Murakami M, et al. Effects of isoproterenol and bmylscopolamine on the friction between an artificial stone and the intraureteral wall in anesthetized rabbits. *J Urol* 2001;166:1083-7. http://dx.doi.org/10.1016/S0022-5347(05)65926-5
8. Hancock AA. Adrenoceptor: A synopsis of their pharmacology and molecular biology. *Drug Dev Des* 1996;39:54-107. http://dx.doi.org/10.1002/(SICI)1098-2299(19960901)39:1<54::AID-DDR7>3.0.CO;2-J
9. Sigala S, Dellabella M, Milanese GC, et al. Alpha1 adrenoceptor subtypes in men juxtavesical ureter: Molecular and pharmacological characterization. *Eur Urol* 2004;3(Suppl):119-22.
10. Wang H, Liu K, Ji Z, Li H. Effect of alpha1-adrenergic antagonists on lower ureteral stones with extracorporeal shock wave lithotripsy. *Asian J Surg* 2010;33:37-41. http://dx.doi.org/10.1016/S1015-9584(10)60007-3
11. Porpiglia F, Ghignone G, Fiori C, et al. Nifedipine versus tamsulosin for the management of lower ureteral stones. *J Uro1* 2004;172:568-71.
12. Resim S, Ekerhicer H, Ciftci A. Effect of tamsulosin on the number and intensity of ureteral colic in patients with lower ureteral calculus. *Int J Urol* 2005;12:615-20. http://dx.doi.org/10.1111/j.1442-2042.2005.01116.x
13. Küpeli B, Irkilata L, Gurocak S, et al. Does tamsulosin enhance lower stone clearance with or without shock wave lithotripsy? *Urology* 2004;64:1111-5. http://dx.doi.org/10.1016/j.urology.2004.07.020
14. Porpiglia F, Desrefanis P, Fiori C, et al. Role of adjunctive medical therapy with nifedipine and deflazacort after shock wave lithotripsy of ureteral stones. *Urology* 2002;59:835-8. http://dx.doi.org/10.1016/S0090-4295(02)01553-4
15. Lee SR, Jeon HG, Park DS, et al. Longitudinal stone diameter on coronal reconstruction of computed tomography as a predictor of ureteral stone expulsion in medical expulsive therapy. *Urology* 2012;80:784-9. http://dx.doi.org/10.1016/j.urology.2012.06.032

Correspondence: Dr. Abdellatif Janane, Department of Urology, University Military Hospital Med V. Hay Ryad, Rabat, Morocco; a.janane@yahoo.fr